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CASE REPORT

Neuropathological and MRI findings in an acute presentation of hemiconvulsion-hemiplegia: A report with pathophysiological implications

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Summary The mechanisms underlying the hemiconvulsion-hemiplegia-epilepsy syndrome (HHE) remain unclear. The current proposed pathogenic mechanism is a neuronal injury induced by venous thrombosis and/or hypoxia. Previous abnormalities of the brain were suggested as underlying mechanism.

Materials and methods: We report a patient who presented acutely with hemiconvulsion-hemiplegia (HH) syndrome, but unfortunately died. We discuss the possible pathophysiology of the HH syndrome and possible therapeutic implications utilizing the data from neuroimaging and pathological studies. Post-mortem examination was performed including immunohistochemistry and electron microscopy of the brain tissue.

Results: The abnormalities in diffusion-weighted imaging indicate cytotoxic edema of the epileptic hemisphere. The pathological studies confirmed a right homogenous hemispheric edema without evidence of any malformation, inflammatory, infectious or metabolic disease. We found axonal damages in the right thalamus confirmed by anti-neurofilament staining.

Discussion: The pathological studies suggest that cytotoxic edema is responsible for neuronal damage. In HH syndrome, two mechanisms playing a role in the development of a later epilepsy could suggest delayed cell death induced by cytotoxic edema and/or thalamic dysfunction causing a disruption of thalamo-cortical circuit. In acute presentation, the use of anti-edema therapy should be discussed to prevent the cell injury.
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Introduction

Hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome is an uncommon consequence of prolonged focal febrile convulsive seizures in infancy and early childhood. It was first described by Gastaut et al.[1] It is characterized by the occurrence of prolonged clonic seizures with unilateral predominance occurring in the course of a febrile illness in a child younger than 4 years, and followed by the development of hemiplegia. Neuroradiological studies showed unilateral edematous swelling of the epileptic hemisphere at the time of initial status, followed by characteristic global cerebral

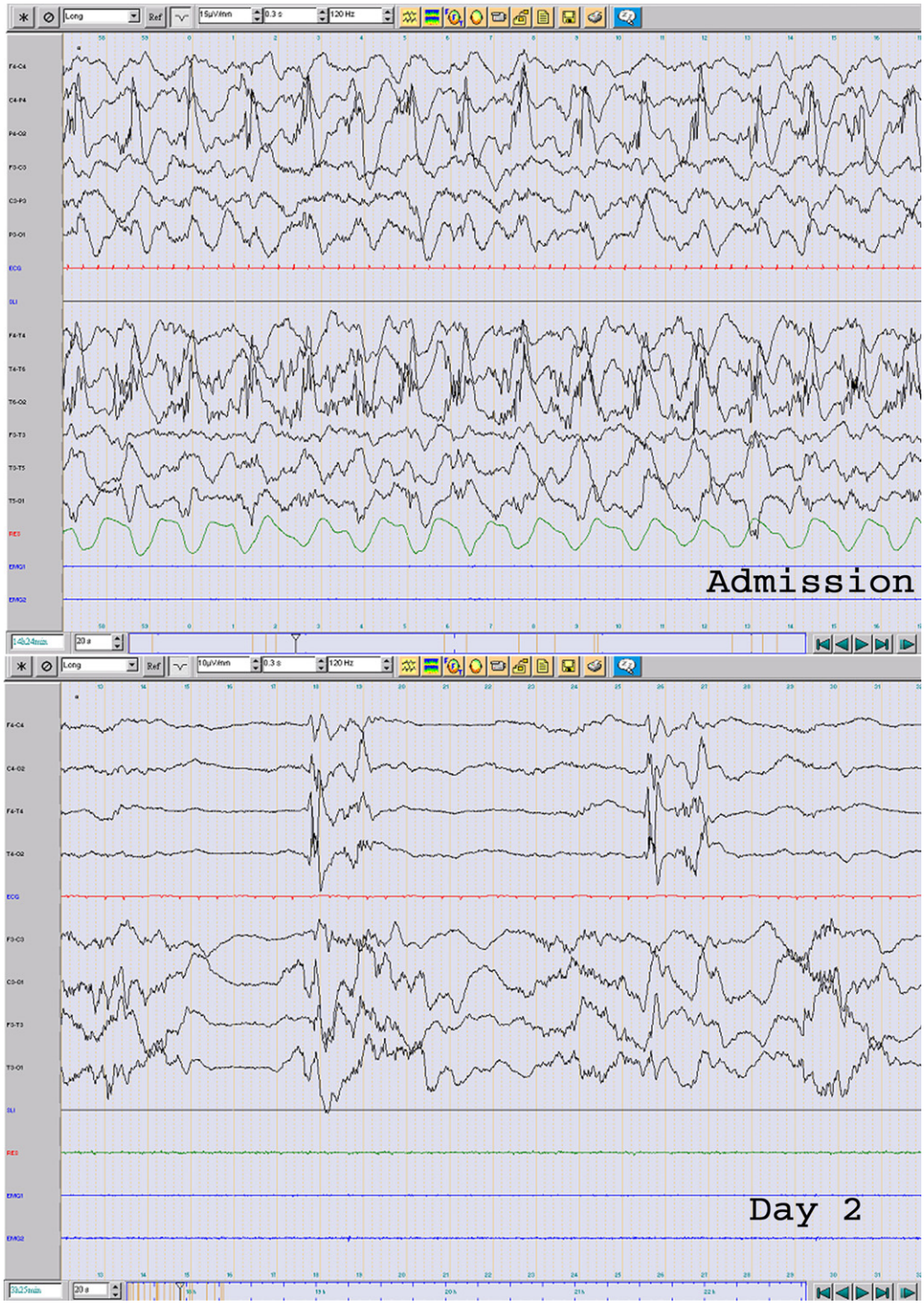

Figure 1 EEG at admission and at day 2. (A) At admission: continuous right hemisphere discharge consisting of rhythmic polyspike-waves. (B) At day 2, discontinuations were observed in the EEG.

hemiatrophy independent of any vascular territory with subsequent appearance of epilepsy.[2,3] Seizures of temporal lobe origin are described as occurring most commonly in this syndrome. The incidence of the syndrome has declined considerably in the industrialized countries over the past 15 years.[4] The accurate management of status epilepticus (especially the introduction of intravenous or rectal diazepam in the early 1960s) may play a role in this decline. The hemiconvulsion-hemiplegia-epilepsy syndrome was reintroduced as a syndrome in the published report of the ILAE Task Force on Classification and Terminology.[5]

The mechanisms underlying the HHE are unclear. The current proposed pathogenic mechanism is a neuronal injury induced by venous thrombosis and/or excitotoxicity.[6] Previous abnormalities of the brain were also suggested as underlying mechanism. We report a patient who presented acutely with hemiconvulsion-hemiplegia (HH) but unfortunately died. We discuss the possible pathophysiology of the HH syndrome and possible therapeutic implications utilizing the data from neuroimaging and pathological studies.

Case report

A 17-month-old girl with a 2-day history of fever treated with acetaminophen presented with prolonged status epilepticus. She had no other significant medical history. The day of her referral, she was found by her mother to be unresponsive and having left hemiconvulsion. The patient was found in the morning (6 h without surveillance). She was given diazepam, phenytoin, phenobarbital and thiopental, which stopped the seizure. She was intubated and transferred to the pediatric intensive care unit. Initial EEG showed right predominant periodic spikes and slow spikes (1 Hz) (Fig. 1A). Routine laboratory investigations and CSF analysis were normal. Cranial CT on the day of admission revealed neither edema nor abnormal tissue densities. At Day 2, a left hemiplegia was noted. The EEG revealed right pseudoperiodic spike-wave complexes (Fig. 1B). Cerebral MRI was performed 5 days after admission (Fig. 2A—D). At Day 5, EEG was characterized by a progressive decrease of cortical activity. At Day 6, the patient presented with a decrease of blood pressure, and without bulbar reflexes. The EEG confirmed the cerebral death.

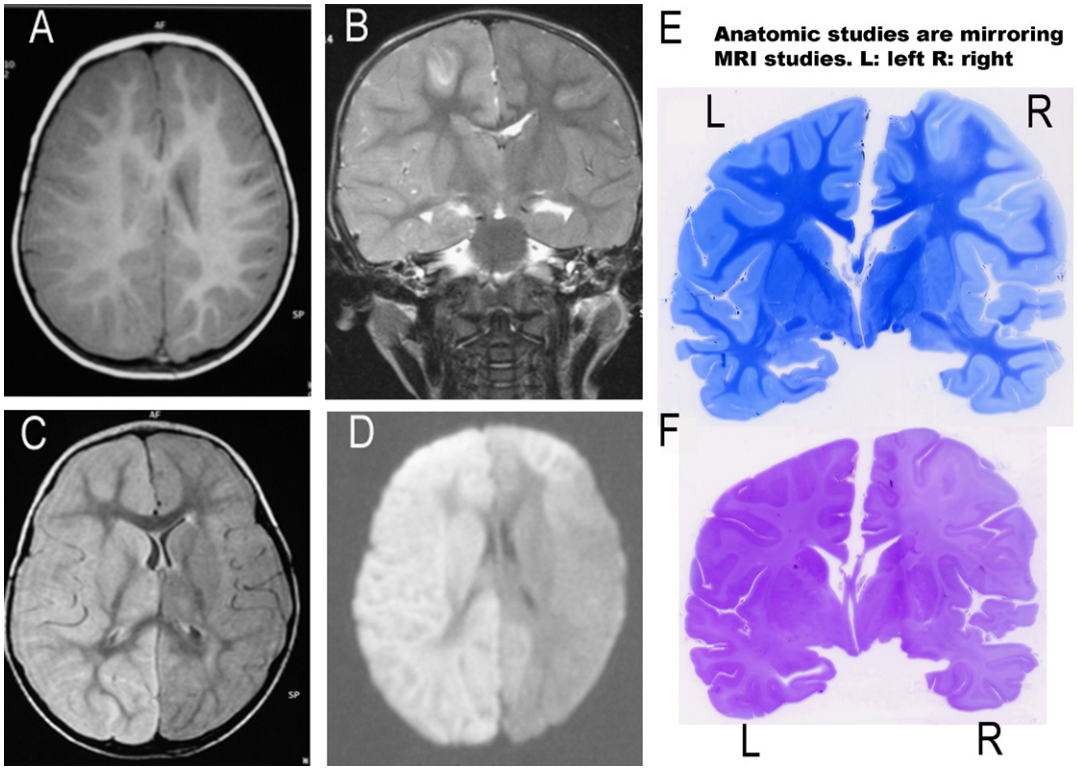

Figure 2 *Brain MRI* (5 days). (A) T1-Weighted, (B) T2-weighted, (C) fluid-attenuated inversion recuperation (FLAIR), (D) diffusion-weighted. Brain MRI shows abnormalities throughout the right hemisphere involving both grey and white matter. The right hemisphere edema was responsible of diffusion abnormalities. *Post-mortem examination* (E) PAS staining of macroscopic view. (F) Lugol staining of macroscopic view. Right (R) hemispheric homogenous edema is observed with both staining.

Materials and methods

MRI study included T1 and T2-weighted, FLAIR and diffusion-weighted axial images and T1 and T2-weighted coronal images.

An autopsy was performed on the patient a few hours after the death. The whole central nervous system, as well as samples of the intrathoracic and abdominal organs was immersed in formalin (2 months). Bilateral samples were taken in associative, primary and limbic cortices, in the hippocampal region, in the diencephalons, brainstem and cerebellum. Paraffin sections were stained with hematoxilin-eosin, lugol and PAS. Neurofilament immunostaining was performed on paraffin sections (monoclonal mouse anti-human neurofilament protein; Dakocytomation, Glostrup, Denmark). Samples taken for electronic microscopy (in the same area cited above) were post-fixed in glutaraldehyde and osmium tetroxide, and embedded in Epon. Sections were examined under a Leo 906 microscope.

Results

Imaging study

MRI performed 5 days (Fig. 2A—D) after admission showed a diffuse right hemispheric high intensity signal in T2-weighted images. Diffusion-weighted imaging revealed a decreased diffusion in the right cortical grey matter, subcortical white matter and right thalamus. There was a decreased diffusion in the left frontal area.

Pathological study

General autopsy did not find any abnormalities

Gross examination and light microscopy of the encephalon

Macroscopic exploration did not find any thrombus, cortical dysplasia or brain malformation. We did not observe any direct or indirect sign suggesting a temporal herniation. There was a right homogenous hemispheric edema (Fig. 2E and F) confirmed with light microscopy examination (Figs. 3B and 4), of each sample when compared to the other side in the same Brodmann area. There was neither microscopic dysplasia, thrombus nor cellular inflammatory response. Right temporal cortex showed spongiosis without cell necrosis or cell apoptosis. Both dentate gyri were normal (Figs. 3A and 4) as well as CA1, CA 2 and CA 3. The occurrence of axonal damages was suggested by an abnormal neurofilament-immunoreactivity in all areas of the right thalamus (Fig. 3C).

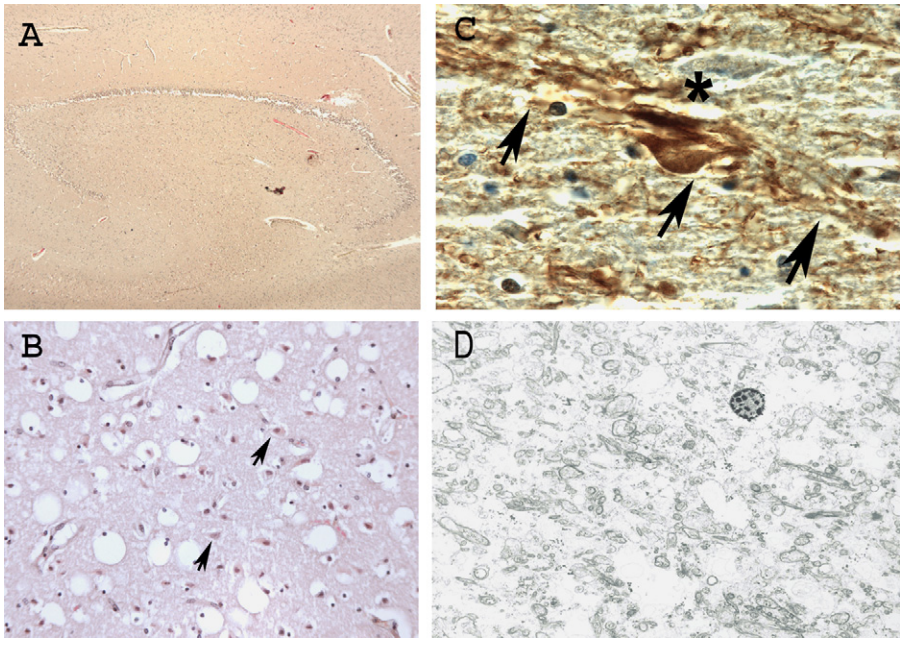

Figure 3 (A) Hematoxylin and eosin staining of dentate gyrus (right temporal lobe; ×25). Dentate gyrus was normal. (B) Hematoxylin and eosin staining of CA2-3 (right temporal lobe; ×400). Spongiosis and edema were observed. Neurons were normal. We did not observe cell death. (C) Immunostaining for neurofilament in the right thalamus (×360). A typical axonal damage is observed (*). Arrows indicate the axon. (D) Electron microscopy study shows edema and spongiosis in the right frontal subcortical white matter (×1260).

Ultrastructural study

Electron microscopy confirmed the hemispheric edema but did not show any cell abnormalities (Fig. 3D).

Discussion

The pathophysiological mechanism in the HHE syndrome remains unknown. The current proposed pathogenic mechanism is a neuronal injury induced by venous thrombosis and/or excitotoxicity. The role of an underlying brain malformation and/or cortical dysplasia was suggested as a trigger of the status. The abnormalities in diffusion-weighted imaging indicate cytotoxic edema confined to the epileptic hemisphere confirmed by the neuropathological studies. The neuropathological studies suggest that the edema is responsible for the neuronal damage. We did not observe any cell death. We suggest that cell damage induced by edema may be the pathophysiological mechanism.

Several neuroimaging studies reporting unilateral edema in HH syndrome were published. Freeman et al. reported three patients who presented acutely and described the early characteristic imaging findings of the HHE syndrome.[7] The neuroradiological findings suggested a diffuse cytotoxic edema confined to the epileptic hemisphere. Two of their three patients presented with diffusion weighted imaging abnormalities. In addition, one of the three patients showed a decrease of the *N*-acetylaspartate peak in magnetic resonance spectroscopy in the injured hemisphere compared to the other side. Diffusion-weighted imaging has primarily been used in the study of cerebral ischemia, where cytotoxic edema is the end result of a number of disrupted cellular metabolic processes including failure of energy-dependent ion transport and increased permeability.[8] There is also a concomitant marked reduction in the apparent diffusion coefficient of water in ischemic tissue. A similar decline in apparent diffusion coefficient of water has been demonstrated both in experimental models and in patients who present in status epilepticus. It has been specially reported in some patient in acute phase of HHE syndrome.[9–11] The decreased diffusion in the left frontal area on diffusion weighted imaging is due to the functional connection of this area to other hemispheric area.

Only Mori's papers had reported neuropathological studies of HHE syndrome.[12,13] The post-mortem

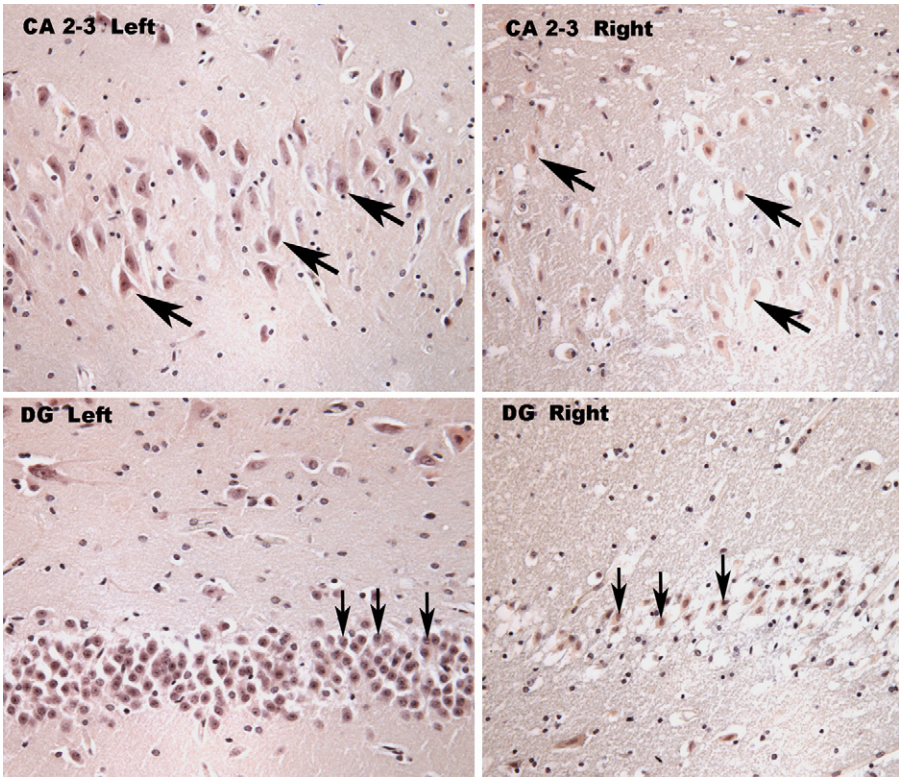

Figure 4 Hematoxylin and eosin staining comparing left and right side of the brain in CA 2–3 and dentate gyrus (×250). On the right side, spongiosis, edema and dissociation of cell layers were observed. Arrows show some granular cells in dentate gyrus and some pyramidal cells in CA2–3.

specimens reported by Mori showed diffuse cortical scarring in the laminae. Only one patient had malformation (polymicrogyria in the left sylvian fissure). He reported the studies of two brains from infants who died several days after hemiconvulsions and/or generalized status epilepticus. In these two patients, CSF was normal and the histological examination did not reveal any inflammatory process or vascular lesions. Diffuse laminar necrosis and edema in cortical layers 3 and 5 extending throughout the hemisphere and including hippocampus were the main histological features.

Neuropathological studies in our case did not find any cell death or underlying conditions. Retraction balls were found in the right thalamus. Anti-neurofilament immunostaining was very useful to determine the existence of axonal damage in our patient. This staining used antisera specific of degenerative neurofilaments.[14]

In status epilepticus, neuronal injury is mediated by excess excitation via activation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors and consequent elevated intracellular calcium that causes acute necrosis and delayed apoptotic cell death.[15] In addition, high intracellular calcium concentrations result in the activation of a large number of calcium dependant processes which may increase cytotoxic edema.

In HH syndrome, it seems that the brain injury is the result of cytotoxic edema caused by a prolonged focal seizure. We excluded in our patient an underlying condition such as thrombosis, brain malformation or cortical dysplasia. The absence of cell death does not exclude this mechanism in the occurrence of a later epilepsy in HHE syndrome. We hypothesize that cell death could appear later after the cytotoxic edema. On the other hand, a thalamic dysfunction induced by cell damages can be responsible for disruption of the thalamo-cortical circuit and can play a role in the later epilepsy. Our findings strongly suggest that the use of anti-edema therapy or NMDA-type glutamate receptors antagonists should be considered to prevent the cell injury in HH syndrome.

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